

Survival of Colorectal Cancer Patients in Singapore by Anatomic Subsite: A Population-based Study[†]

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Abstract

Introduction: Studies of the prognostic value of anatomic subsite in colorectal cancer survival have yielded conflicting results. Two explanations for possible differences in survival patterns between proximal and distal lesions in the colorectum are biological difference between subsites and the presence of more early-stage lesions in distal than in proximal large bowel. **Materials and Methods:** A total of 435 cases with proximal lesions and an equal number with distal lesions diagnosed between 1990 and 1992 were randomly selected from the Singapore Cancer Registry. Information on vital status at 31 December 1996 were obtained by computerised matching with data from the National Registry of Births and Deaths. **Results:** Persons with proximal cancers in our study population did not present at a later stage than persons with distal cancer, local lesions (Dukes' Stage A + B) being 45.5% and 45.1%, respectively. Our analysis showed no significant differences in survival between subsites on a stage-for-stage basis. The 5-year survival rates were 42% and 44% for proximal and distal lesions, respectively (median survival times 3.98 and 4.27 years). Stage at diagnosis was the strongest predictor of survival. Among proximal lesions, 5-year survival rates were 57%, 36% and 12% for local, regional and metastatic lesions, respectively. The corresponding figures for the distal group were 65%, 37% and 10%. Age at diagnosis had a significant influence on survival. **Conclusions:** Our results, based on population-based figures on survival of colorectal cancer patients where the impact of screening has not been large, do not support an independent influence of anatomic subsite in predicting survival of colorectal cancer.

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Key words: Colorectal cancer, Distal, Population-based cancer registry, Proximal, Survival

Introduction

Colorectal cancer incidence rates rank second in most developed countries and have been rising rapidly in urban societies of East Asia.^{1,2} Despite much effort to detect early-stage disease and to explore more effective treatment methods, the overall 5-year survival rate has remained around 40% based on the reports from European populations and the United States' Surveillance, Epidemiology, and End Results (SEER) analysis from 1983 to 1988.³

Among the prognostic variables which have been investigated extensively, only stage at diagnosis has been consistently identified as an important predictor of survival.⁴⁻⁷ Anatomic subsite of colorectal cancer has been regarded as a possible prognostic factor in determining survival in several studies,^{6,8-11} but the mechanism is uncertain. Two possible reasons have been put forward. First, colorectal

cancer is not a unique entity because proximal and distal cancers are different possibly in genetic and environmental epidemiology.^{5,12-14} Second, the observed difference in prognosis may have been a result of a difference in the stage at diagnosis between subsites, in that distal lesions tend to be diagnosed earlier by improved early detection capabilities and the widespread introduction of screening methods such as sigmoidoscopy in the West^{6,15} where most of these studies have been conducted to date.

Singapore is an island republic with a resident population of 3.1 million, of which 77% are Chinese, 14% Malays and the remainder of Indian or other origin¹⁶ Along with rapid economic development and industrialisation, Singapore, just like some other Asian countries, has experienced a rapid increase in colorectal cancer incidence over the past few decades.² Colorectal cancer has been one of the most

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commonly diagnosed cancers in both males and females since 1983 in the local population, with incidence doubling between 1968 and 1992.¹⁷ Although screening by endoscopy has been available to the general public since 1985, it is not widely applied to asymptomatic persons, nor has it been incorporated into professional guidelines or public education materials by the Ministry of Health. Given that the impact of these early detection methods is likely to be significantly lower than in the West, a different pattern in colorectal cancer survival by subsite from the findings in some Western countries may be expected.

Data on colorectal cancer survival by subsite in Asian populations are currently sparse or have been derived from hospital series. The objective of this study was to determine colorectal cancer survival rates by anatomic subsite in Singapore, and to evaluate the effect of anatomic subsite value and other known predictors on survival using population-based data.

Materials and Methods

Classification of Subsite

For the purposes of this study, the site of anatomical origin constituted a key analytic variable. Proximal and distal subsites were defined according to differences in embryological origin, function and pathogenetic mechanism.^{12,18} The point of anatomic division chosen—between the transverse colon and the splenic flexure—has been widely used in many epidemiological studies. Hence, the caecum, ascending colon, hepatic flexure and transverse colon form the “proximal” subsite in this study, while the rest of the large intestine including the splenic flexure, descending colon, sigmoid colon and rectum, form the “distal” subsite. Synchronous tumours which involved both distal and proximal colon were excluded from the analysis.

Selection of Study Population

The Singapore Cancer Registry was set up in 1968 with the aim of collecting basic information on all incident cancers occurring in the population of Singapore. The registration procedure has been well-documented elsewhere.¹⁹ Between 1 January 1990 to 31 December 1992, there were in total 435 proximal and 2202 distal colorectal cancer cases comprising residents of Chinese, Malay and Indian origin. As the main purpose of this study was the comparison of survival between subsites, we included all 435 proximal cases and randomly selected an equal number of distal cases among all distal cases notified in this period. Among the cases, 31 (4%) subjects were found to be registered by death certificates only (DCO), for which survival time was unknown. These cases were excluded from the analysis.

Personal and Clinical Variables

Basic demographic data (ethnicity, gender, age at diagnosis, date of diagnosis, anatomic location) for all study subjects were abstracted from the Singapore Cancer Registry database. To obtain information on clinical stage at diagnosis, permission was obtained from the relevant hospitals to retrieve and review all patients' medical reports. Altogether, 828 cancer cases (98.7%) were uniformly staged using surgical and pathological findings in the medical reports.²⁰

Date and cause of death for all study subjects were obtained by computer linkage with the National Birth and Death Registry database up to 31 December 1996. For surviving patients, the date of last appointment recorded in the medical records was also retrieved. Survival was measured from diagnosis to 31 December 1996. To adjust competitive risks of death from causes other than colorectal cancer, which vary considerably among different age groups, cases who died from other causes were considered “withdrawn alive” at time of death and were censored. As death registration is a legal requirement and Singapore is a small and densely populated country, the information in terms of vital status and date of death is considered virtually complete.

Data Analysis

To explore the association between subsite and other variables, percentages and chi-square tests of independence were computed. The actuarial life-table method was used to obtain colorectal cancer-specific 5-year survival rates for univariate analysis, and the log-rank test to compare survival distribution by subgroups.²¹

Multivariate analysis using the Cox regression model was also performed to evaluate the role of each factor after adjusting for the effects of the remaining prognostic factors.²² The model relies on the assumption that the ratio of the estimated hazard across time is a constant. In our study, all covariates were coded using indicator variables. No violations of the proportional hazard assumption for the covariates were found when tested by log-minus-log survival plot.²¹ The Cox regression analysis was performed using the backward stepwise procedure, in which all variables initially were included in the model, then those having the highest *P* value (>0.05) were removed stepwise from the model, until only those with independent effects on survival remained.

All analyses were performed using the SPSS 8.0 statistical package.

Results

A total of 839 subjects were included in the study, of which 413 had proximal cancers and 426 distal cancers. Of

the 839 cases, 19 cases (2.3%) were lost to follow-up after a known date; 451 cases (53.8%) had died from colorectal cancer and 23 cases (2.7%) had died from causes other than colorectal cancer, while 346 (41.2%) cases were still alive on 31 December 1996.

Characteristics of Study Population by Subsite

The distribution of characteristics of colorectal cancer cases stratified by subsite, is summarised in Table I. In both proximal and distal groups, there were more than 90% cases from Chinese and less than 5% from Indians. Compared with proximal lesions, distal lesions had a significantly higher proportion of Malays (6.8% for distal vs 5.1% for proximal lesions) and lower proportion of Indians (1.4% for distal and 4.4% for proximal lesions). Distribution by ethnicity differed significantly between subsites ($P = 0.024$).

There was no difference in gender distribution between proximal and distal cases ($P = 0.44$). Among proximal cancers, the proportions of very young (<40 years) and very old (≥ 70 years) cases were higher than among those with distal cancers (6.5% and 40.0% vs 3.1% and 32.6%, respectively) ($P = 0.002$).

With regard to the extent of disease using TMN classification, the subjects were distributed as follows: localised cases (Stage I + Stage II) about 45% to 46%, regional spread (Stage III) 32% to 34%, distant metastasis (Stage IV) about 20% and information not available 1.2% to 1.5% in both subsites. Surprisingly, we did not observe more early-stage lesions among cases with distal cancers.

TABLE I: CHARACTERISTICS OF STUDY POPULATION BY ANATOMIC SUBSITE

	Proximal		Distal		<i>P</i> value*
	No. of subject	Percentage (%)	No. of subject	Percentage (%)	
Gender					
Male	211	51.1	230	54.0	0.440
Female	202	48.9	196	46.0	
Age at diagnosis					
<40	27	6.5	13	3.1	0.002
40-69	221	53.5	274	64.3	
≥ 70	165	40.0	139	32.6	
Ethnicity					
Chinese	374	90.6	391	91.8	0.024
Malay	21	5.1	29	6.8	
Indian	18	4.4	6	1.4	
Extent of disease					
Local (Stage A + B)	186	45.1	194	45.5	0.939
Regional (Stage C)	134	32.4	143	33.6	
Metastatic (Stage D)	87	21.1	84	19.7	
Not staged	6	1.5	5	1.2	

* χ^2 -test of overall association

Determinants of Survival

The overall colorectal cancer-specific 5-year survival rates were 42% for proximal cancers and 44% for distal cancers. The corresponding median survival times were 3.98 years and 4.27 years, respectively.

The colorectal cancer-specific survival curves for both proximal and distal cases using the life-table method are shown in Figure 1. Patients with proximal lesions appeared to have a significantly higher risk of death in the first two years from diagnosis. Subsequently, the proximal curve approximated the distal curve. In spite of this, the overall comparison in survival between these two groups by log-rank test was not statistically different ($P = 0.43$).

When subsites were compared on a stage-for-stage basis (Fig. 2), survival curves for cases with proximal lesions tended to drop more rapidly than those for cases with distal lesions, especially for local disease. However, the observed difference was not statistically significant at all stages by the log-rank test with P values being 0.07, 0.56 and 0.22 for local, regional and distal diseases, respectively. In this analysis, non-staged cases were excluded due to the small number in this group.

The effects of other variables on survival are summarised in Tables IIa and IIb. Prognosis in both groups was strongly related with age at diagnosis. Median survival time decreased monotonically from young (age <40) to very old group (age ≥ 70): 6+, 4.57 and 2.11 years for proximal cases, 3.5, 4.72 and 2.50 years for distal cases. The elderly appeared to have the worst survival for both subsites.

Gender and ethnicity were not significantly related to prognosis, but it should be noted in this regard that there were small numbers of cases among Malays and Indians.

As expected, survival was strongly related to clinical

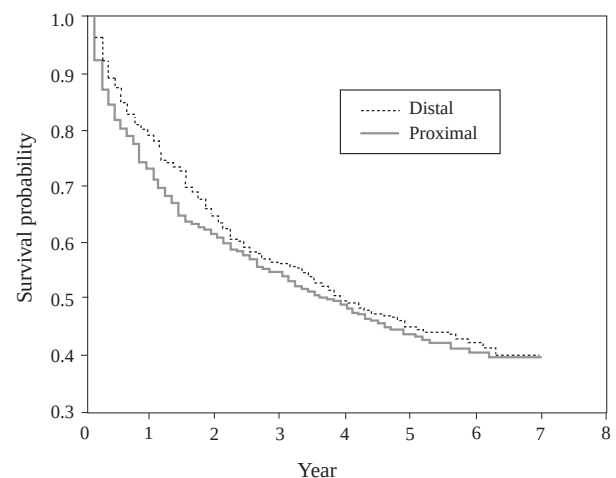


Fig. 1. Colorectal cancer specific survival curves of proximal cancer patients ($n = 413$) and distal cancer patients ($n = 426$) by life-table method

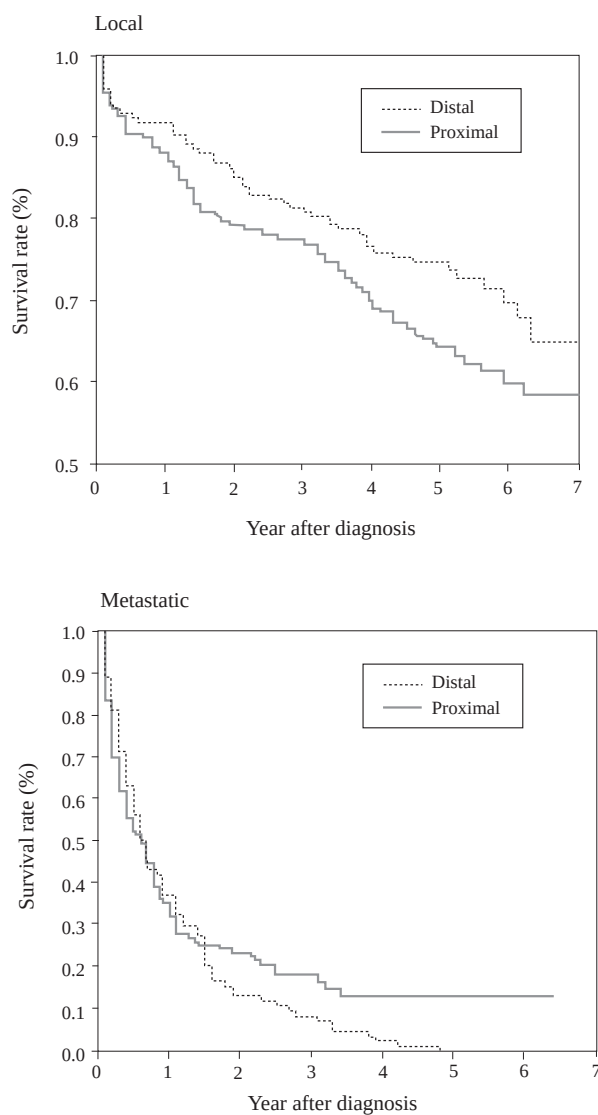


Fig. 2. Colorectal cancer specific survival curves for proximal and distal cases on a stage-for-stage basis by life-table method (*P* values by log rank test are 0.07, 0.56 and 0.22 for local, regional, and metastatic disease, respectively)

stage at diagnosis. Persons with metastatic disease at diagnosis had the worst survival while localised tumours led to the best prognosis ($P < 0.01$). The 5-year survival rates reduced progressively from local to metastatic disease, being around 60%, 35% and 10% for local, regional and metastatic diseases, respectively. The findings were consistent for both subsites.

Multivariate Analysis of Survival

All variables previously considered were included in a proportional hazards regression model. In Table III, the risks of dying for all the variables (subsite, gender, age at diagnosis, ethnicity and stage at diagnosis) considered in the model are shown as crude and adjusted relative risks after allowing for the effect of other variables. Stage at

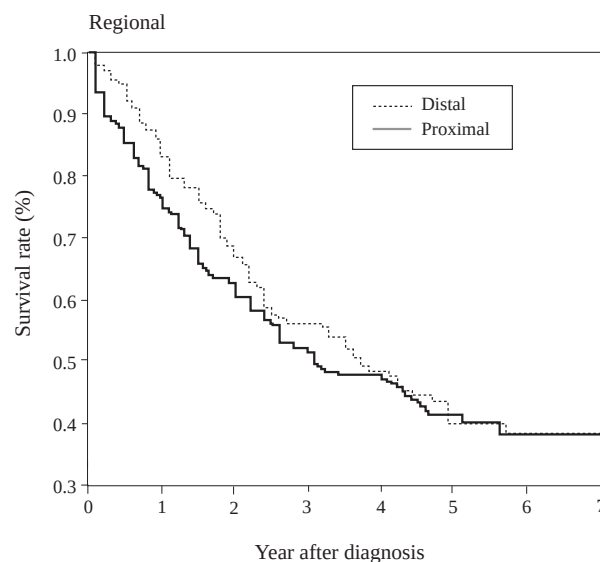


TABLE IIa: COLORECTAL CANCER SPECIFIC 5-YEAR SURVIVAL RATE (%) AND MEDIAN SURVIVAL TIME AMONG CASES WITH PROXIMAL LESIONS ($n = 413$) BY GENDER, BROAD-AGE GROUP, ETHNICITY AND AGE AT DIAGNOSIS

	No. of cases	Median survival time (y)	5-year survival (%)	<i>P</i> value
Gender				
Male	211	3.73	41	0.96
Female	202	4.24	38	
Age at diagnosis				
<40	27	6+	74	<0.001
40-69	221	4.57	45	
≥70	165	2.11	28	
Ethnicity				
Chinese	374	3.83	41	0.41
Malay	21	4.34	45	
Indian	18	6+	60	
Extent of disease				
Local (Stage A + B)	186	6+	57	<0.001
Regional (Stage C)	134	3.14	36	
Metastatic (Stage D)	87	0.74	12	

diagnosis and age at diagnosis maintained their significant effects in predicting survival after controlling for the effects of other variables. In comparison to the reference category (localised disease), regional cases had more than two times higher risk of dying, while the risk increased more than eight-fold for metastatic cancers.

The effect of age at diagnosis was not significantly modified by adjusting for the other variables. In comparison to those in the 40-69 years age group, the adjusted relative risk in the elderly is 1.45 times higher (95% CI: 1.20-1.76), but no significant difference in survival between the young (<40) and those in the 40-69 years age group was detected.

TABLE IIb: COLORECTAL CANCER SPECIFIC 5-YEAR SURVIVAL RATE (%) AND MEDIAN SURVIVAL TIME AMONG CASES WITH DISTAL LESIONS (n = 426) BY GENDER, BROAD-AGE GROUP, ETHNICITY AND AGE AT DIAGNOSIS

	No. of cases	Median survival time (y)	5-year survival (%)	P value
Gender				
Male	230	3.76	38	0.26
Female	196	4.34	45	
Age at diagnosis				
<40	13	3.50	38	<0.05
40-69	274	4.72	47	
≥70	139	2.50	32	
Ethnicity				
Chinese	391	4.53	45	0.09
Malay	29	2.15	26	
Indian	6	5+	67	
Extent of disease				
Local (Stage A + B)	194	6+	65	<0.001
Regional (Stage C)	143	3.58	37	
Metastatic (Stage D)	84	0.79	10	

Subsite and gender still showed no significant effects after adjusting for other covariates. Compared to the univariate analysis on survival by subsite, the subsite differences became much smaller after statistically controlling for the effects of other covariates, the hazard ratio for distal cases being 0.97 (95% CI: 0.81-1.17), when proximal cases were considered as the reference group

The similarity in survival pattern in both subsites after adjustment for other covariates can be observed in Figure 3. It shows theoretical survival curves of colorectal cancer patients by subsite simultaneous adjustment for all other variables, computed by the Cox model. Compared to the curves in the unadjusted model (Fig.1), the two curves become closer and almost overlap.

Discussion

In summary, our results show no significant differences in survival rate between proximal and distal colorectal cancers after controlling for other prognostic factors; the 5-year survival rate is approximately 40% for both subsites. Clinical stage at diagnosis is the strongest predictor of survival. For both subsites, the estimated 5-year survival rates are about 60%, 35% and 10% for local, regional and metastatic lesions, respectively.

The present study has the advantage of using all proximal cases and a random sample of distal cases taken from the population-based data in the same period, thus avoiding any possible selection bias that may occur in a hospital-based series. On the other hand, studying a sample of cases allowed us to be able to check and supplement important

TABLE III: RELATIVE RISK (RR) OF MORTALITY (95% CI) ESTIMATED FROM MULTIVARIATE ANALYSIS

Variable	No. of cases	Crude		Adjusted*	
		RR	95% CI	RR	95% CI
Subsite					
Proximal	413	1.00	-	1.00	-
Distal	426	0.93	(0.77, 1.12)	0.97	(0.81, 1.17)
Gender					
Male	441	1.00	-	1.00	-
Female	398	0.93	(0.77, 1.12)	1.00	(0.83, 1.20)
Age at diagnosis					
40-69	495	1.00	-	1.00	-
<40	40	0.71	(0.42, 1.20)	0.61	(0.36, 1.02)
≥70	304	1.50	(1.24, 1.81)	1.45	(1.20, 1.76)
Ethnicity					
Chinese	765	1.00	-	1.00	-
Malay	50	1.64	(0.85, 3.17)	1.43	(0.99, 2.07)
Indian	24	2.10	(1.00, 4.42)	0.87	(0.44, 1.69)
Extent of disease					
Local	380	1.00	-	1.00	-
Regional	277	2.24	(1.77, 2.83)	2.27	(1.79, 2.87)
Metastatic	171	8.24	(6.43, 10.55)	8.31	(6.47, 10.67)

* Estimated by adjusting each variable for the other

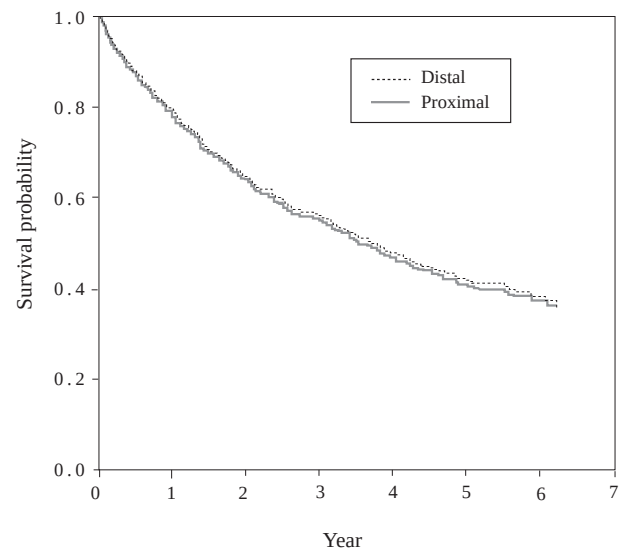


Fig. 3. Theoretical survival curves for cases with proximal lesions and cases with distal lesions after controlling for other covariates (age at diagnosis, gender, ethnicity and stage at diagnosis) by the Cox regression model.

information, such as stage at diagnosis, by retrieving and consulting all relevant medical records, which were normally not recorded in population-based registry data file. This was an important factor in the validity of the information used in this study.

Secondly, the two primary sources of data—the Singapore Cancer Registry and the Registry of Births and Deaths—are recognised to be complete, by virtue of the small size of

the country, ease of medical access and good record linkage.

The potential limitations should also be considered. We excluded cases with “subsite unspecified”, and these may have a poorer continuity of care and other quality-related measures than those cases with subsite specified.²³ Survival analysis without taking account of this subgroup of patients could result in an over-estimation of colorectal cancer survival rate. In the Singapore Cancer Registry, however, only 6.6% of patients among all incident cases had an unspecified colorectal cancer tumour location, and we believed that the small fraction could not produce important effects on overall survival of colorectal cancer.

Colorectal cancer survival rates in our study are similar to those reported in Western countries.²⁴ Other population-based studies have reported overall 5-year survival rates of between 37% and 54%.³ Our findings are also consistent with a previous local hospital-based case-series which reported a 5-year survival rate of 71%, 55%, 36% and 16% for the respective clinical stages.²⁵

We found, not unexpectedly, that the strongest predictor of survival is clinical stage at diagnosis. The role of stage at diagnosis as the single most important determinant of survival has been previously reported.⁴⁻⁷ Typically, the 5-year survival rates reported for Stage I and II in these studies were more than 70% and for Stage III around 30% and Stage IV around 10%.⁴⁻⁷ These are slightly higher than those in our population.

Our results indicate a lack of effect of subsite on survival. This may be related to the stage distribution of cases in this population. Several studies have pointed out that distal cancers present with more early-stage disease than proximal cancers.^{6,15,26} This is largely attributed to the fact that early diagnostic capabilities play a more important role in distal rather than proximal cancers due to easier access, for example, by sigmoidoscopy. Thus, the different survival patterns between proximal and distal large bowel cancer in these studies may be mainly due to the lead-time bias for distal lesions, whose diagnoses were made approximately 6 months earlier than cases with proximal cancer based on population-based reports from Italy.⁶ In the current study, there is no significant difference in stage distribution between the two subsite groups, the percentage being around 45%, 33% and 20% for local, regional and metastatic lesions, respectively. This may be partly explained by the fact that routine endoscopy and endoscopic polypectomies in larger bowel began much later in Singapore compared with Western countries.

In our study, 6.5% of the proximal cases occurred in those below the age of 40 years old compared to 3.1% in distal cases. This may reflect to some extent the predilection of familial cancers (such as hereditary nonpolyposis colorectal cancers), which usually occur at an earlier age,

for the proximal colon.²⁷⁻²⁹ Unfortunately, we did not have information on family history to examine this possibility.

The effect of age on the prognosis of patients with colorectal cancer is somewhat controversial. Various studies have suggested that colorectal cancer in patients below the age of 40 years is an especially poor prognostic sign,^{6,30} because these patients present with more advanced disease and with a poorer histology grade of differentiation. However, this is not corroborated by other studies,^{31,32} which demonstrated that the outcome in younger patients was similar to that in older patients and that there was no difference in stage distribution between younger patients and older patients. In our study, those who were 70 years and above at diagnosis experienced a poorer survival, with a relative risk of mortality 1.45 times that of those between the ages of 40 to 69 years, after adjusting for other variables, including stage at diagnosis. The differences among the age groups could not be explained in terms of higher mortality from other causes in younger age group, as the colorectal cancer-specific survival rates obtained in this study have been adjusted for the difference in mortality from all causes. A similar observation has been reported in the UK.³³ On the other hand, sepsis and complications of surgery have been reported to be more frequent in the elderly³⁴ and may result in a higher rate of postoperative mortality in this age group.

The present study thus provides, for the first time, figures on survival of colorectal cancer by subsite in an Asian population. The independent prognostic variables identified through the present analysis may offer some useful information on prognostic advice and in evaluating the treatment results. A larger population-based study, which will examine these issues in more detail, is also underway.

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